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The voluntary imagination impairment in ASD linked to the neuropeptide N-Acetyl-aspartyl glutamate imbalance on cingulated cortices.

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Graphical Abstract
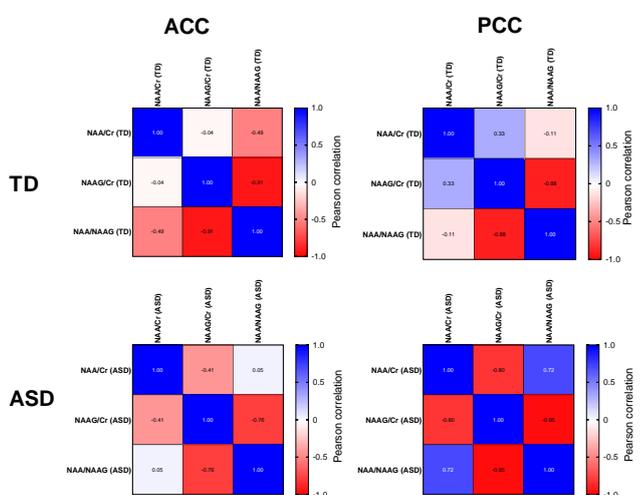
Figure 1 Correlation between ´Imagination´ and NAA/Cr, NAAG/Cr, NAA/NAAG ratio in ASD and TD groups in cingulated cortices (ACC, PCC).

Abstract.

Background: Autism is defined neurodevelopmental disorder characterized by significant impairments in social interaction, and imagination as symptoms highlights. Recently have described been the differences of brain function in voluntary and involuntary imagination. Although, individuals with moderate to severe autism spectrum disorder (ASD) usually manifest a range of deficits related to the voluntary imagination network, its neurological etiology follow unclear. The AQ is a psychometric test has five developmental domains to assess autistic characteristics in adults (social, communication, imagination, attention to detail and, attention switching/tolerance of change) and, in this study we will focus on the domain of 'Imagination', that is directly related to the development of social skills in healthy subjects. Previously, we had described been the altered N-Acetyl-aspartyl-glutamate (NAAG) levels found in anterior (ACC), and Posterior (PCC) cingulated cortices by 1H-MRS in individuals with ASD that suggested the neuronal damage. In this sense and following our research line linked to the
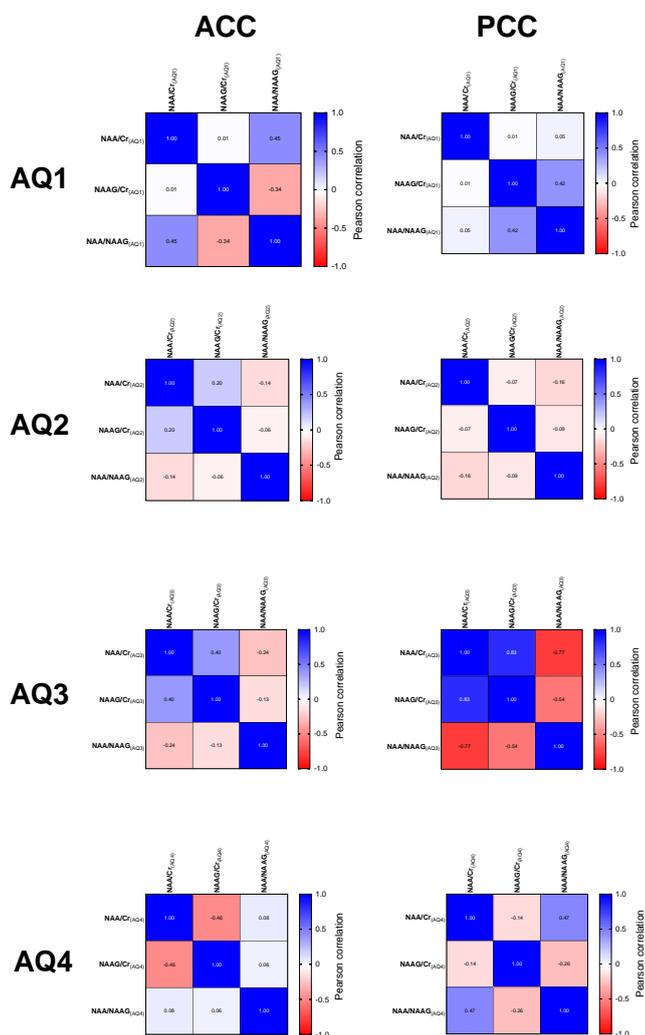
Figure 2 *Correlation between ´Imagination´ and NAA/Cr, NAAG/Cr, NAA/NAAG ratio in ASD severity by AQ-score by AQ groups (AQ1, A2, AQ3, and AQ4) in cingulated cortices (ACC, PCC).*

Table 1 *Pearson's correlation between 'Imagination' and, NAA/NAAG ratio in ACC, and PCC. ASD and TD groups were compared.*

Brain areas ratios	ASD (n = 21)		TD (n = 42)	
	r	p	r	p
ACC				
NAA/Cr	0.0594	0.7981	0.0981	0.5470
NAAG/Cr	0.1135	0.7891	- 0.2698	0.3123
NAA/NAAG	0.0769	0.8564	0.5203	0.1510
PCC				
NAA/Cr	0.3758	0.0931	- 0.1134	0.4859
NAAG/Cr	- 0.4936	0.1769	- 0.1270	0.6271
NAA/NAAG	0.4672	0.2048	- 0.1410	0.6976

neuropeptide NAAG as a key mechanism underlying symptoms of ASD, arise the hypothesis of NAA-NAAG metabolism imbalance and their relationship with impairments of the imagination in autism, which lead the next step in our investigation to correlate NAAG imbalance linked to cingulated cortices with the imagination skills in ASD.

Aim: *To study the participation of neuropeptide NAAG metabolism in the cingulated cortices correlated with the AQ domain 'Imagination' associated with ASD severity using 1H-MRS.*

Methods: *The methodology used in the development of this study was ordered according to the importance of the studies carried out, which led us to the reported results. We quantified NAAG, and NAA signal in ACC and, PCC separately from the 1H-MRS assessed in 22 patients with ASD and 44 healthy comparison subjects, matched for age, on a 3.0 Tesla MR scanner. Autism quotients (AQ) scores were assessed. Statistic one-way ANOVA was applied. Furthermore, the Pearson correlation hallmarks the goal.*

Results: *The results of the Pearson correlation were represented graphically, where it was observed that there is positive low correlation between the AQ domain 'Imagination' and NAAG/Cr (r = 0.1135, p = 0.7891) in ACC, and moderate positive correlation with NAA/Cr (r = 0.3758, p =0.0931), and NAA/NAAG (r = 0.4672, P = 0.2048) in ASD group ratio in the PCC (see Table 1, Fig.1). In contrast to TD group, the correlation coefficient was negative. However, when was stratified ASD plus TD groups as AQ1, AQ2, AQ3, and AQ4 subgroups, was shown a moderate negative correlation between 'Imagination' and NAAG/Cr (r = - 0.5083, p = 0.0761) in AQ4 (see Table 2, Fig. 2) in ACC, in contrast to AQ1 (control group). Nonetheless in PCC was found a low positive correlation between 'Imagination' and NAAG/Cr (r = 0.2629, p = 0.5689), and NAA/NAAG (r =*

Table 2 *Pearson's correlation between 'Imagination' and, NAA/Cr, NAAG/Cr, NAA/NAAG ratios in cingulated cortices (ACC, PCC). AQ1, AQ2, AQ3, and AQ4 groups were compared.*

Brain areas ratios	NAA/Cr r	p	NAAG/Cr r	p	NAA/NAAG r	p
AQ1						
ACC	-0.2978	0.3471	0.3174	0.3148	-0.1911	0.5518
PCC	0.1792	0.5773	-0.4074	0.1886	-0.4817	0.8818
AQ2						
ACC	-0.1090	0.6207	0.4921	0.0171	0.1883	0.3897
PCC	0.1449	0.5095	-0.2456	0.2586	-0.0805	0.7150
AQ3						
ACC	0.2801	0.5429	0.2629	0.5689	-0.0411	0.9303
PCC	0.0947	0.8399	0.2629	0.5689	0.0017	0.9970
AQ4						
ACC	0.1056	0.7312	-0.5083	0.0761	-0.3313	0.2688
PCC	-0.0468	0.8794	-0.5083	0.0761	0.4724	0.1031

0.0017, p = 0.9970) in AQ3, but in AQ4 a moderate positive correlation between 'Imagination' and NAA/NAAG (r = 0.4724, p = 0.1031). Highlighting, that AQ2, AQ3, and AQ4 groups maintain a pattern correlation to 'Imagination' different than the AQ1 group that was considered (below the mean of autistic characteristics) as a group of healthy subjects that indicate disturbed metabolism. These results make us suggest the relation of imagination deficit with severity in ASD symptoms in PCC, and its correlation with NAA-NAAG metabolism imbalance (Crespi, Bernard, et al, 2016); who considered that Imagination exhibits the strongest male bias of all Autism Quotient (AQ) subscales, in non-clinical populations.

Conclusion: The opportunity to measure the concentration of NAAG by 1H-MRS in the cingulate cortices creates a new and promising approach for intensified research on this neuropeptide systems, and development of novel drug candidates in ASD.

Keywords: Autism spectrum disorders; Cingulated cortices; Autism Quotient (AQ) subscales; Imagination; 1H-MRS

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